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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/683,803	10/10/2003	Roberto Crea	112448.00003 ORD	2158

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EXAMINER	
ROYDS, LESLIE A	

ART UNIT	PAPER NUMBER
1614	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/683,803	Applicant(s) CREA, ROBERTO	
	Examiner Leslie A. Royds	Art Unit 1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.
2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.
3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-15 is/are pending in the application.
4a) Of the above claim(s) _____ is/are withdrawn from consideration.
5)☐ Claim(s) _____ is/are allowed.
6)☒ Claim(s) 1-15 is/are rejected.
7)☐ Claim(s) _____ is/are objected to.
8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.
10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a)☐ All b)☐ Some * c)☐ None of:
1.☐ Certified copies of the priority documents have been received.
2.☐ Certified copies of the priority documents have been received in Application No. _____.
3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 2 January 2004.
4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-15 are presented for examination.

Acknowledgement is made of Applicant's claim for priority under 35 U.S.C. 119(e) to U.S. Provisional Patent Application No. 60/417,838, filed October 11, 2002. Applicant's Information Disclosure Statement (IDS) filed January 2, 2004 has also been received and entered into the application. As reflected by the attached, complete copy of form PTO/SB/08A (two pages total), the Examiner has considered the cited references.

Applicant's Claim for Priority Under 35 U.S.C. §119(e)

The complete disclosure of U.S. Provisional Patent Application No. 60/417,838, filed October 11, 2002, to which the present application claims benefit under 35 U.S.C. §119(e) has been considered. Sufficient support and enablement as required under 35 U.S.C. 112, first paragraph, for the presently claimed subject matter has been noted. Accordingly, for the purposes of examination and the application of prior art, the effective filing date of the present application is considered to be the filing date of U.S. Provisional Patent Application No. 60/417,838 (October 11, 2002).

Objection to the Specification

The Examiner has noted the incorporation by reference of *Int J of Pharm*, 33:201-217, 1986 at page 10, lines 7-8 of paragraph [0029] of the disclosure. The incorporation of essential material in the specification by reference to an unpublished U.S. application, foreign application or patent, or to a publication is improper. Applicant is required to amend the disclosure to include the material incorporated by reference, if the material is relied upon to overcome any objection, rejection, or other requirement imposed by the Office. The amendment must be accompanied by a statement executed by the applicant, or a practitioner representing the applicant, stating that the material being inserted is the material previously incorporated by reference and that the amendment contains no new matter. Please see 37 C.F.R. 1.57(f).

Claim Rejection - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12 and 14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of tissue damage caused by free radicals due to environmental pollution; brain or myocardial lesions induced by free radicals following cerebral or myocardial ischemia and attendant reperfusion; diabetic or toxic neuropathies; or metabolic disorders of glucose utilization; does not reasonably provide enablement for the prevention of the same. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

In this regard, the application disclosure and claims have been compared per the factors indicated in the decision *In re Wands*, 8 USPQ2d 1400 (Fed. Cir., 1988) as to undue experimentation. The factors include:

1) the nature of the invention;
2) the breadth of the claims;
3) the predictability or unpredictability of the art;
4) the amount of direction or guidance presented;
5) the presence or absence of working examples;
6) the quantity of experimentation necessary;
7) the state of the prior art; and,
8) the relative skill of those skilled in the art.

The relevant factors are addressed below on the basis of comparison of the disclosure, the claims and the state of the prior art in the assessment of undue experimentation. For the purposes of consideration under 35 U.S.C. 112, first paragraph, the Examiner has focused on the particular condition of metabolic syndrome as characteristic of a "metabolic disorder of glucose utilization" as recited in present claim 12. However, the reasons stated here concerning the burden of enabling the prevention of metabolic syndrome apply also to myriad of other conditions encompassed by claim 12, but for the obvious difference in the type of disorder.

Factors 1 and 2) The claimed invention is directed to methods of preventing tissue damage due to free radicals generated by environmental pollution; of preventing brain or myocardial lesions induced by free radicals following cerebral or myocardial ischemia and attendant reperfusion; of preventing diabetic or toxic neuropathies; or metabolic disorders of glucose utilization; comprising the administration of a composition comprising acetyl-L-carnitine or a salt thereof, a carnitine compound selected from L-carnitine, propionyl-L-carnitine, valeryl-L-carnitine, isovaleryl-L-carnitine or salts or mixtures thereof and also comprising a mixture of polyphenols containing hydroxytyrosol.

Factors 3 and 7) In particular, one skilled in the art could not practice the presently claimed subject matter without undue experimentation because the artisan would not accept on its face that metabolic syndrome could be effectively prevented by administration of the claimed active agent(s). Based on the state of the art, as discussed below, the artisan would have only accepted that the incidence of such a condition could be reduced, rather than that it could actually be prevented from ever occurring.

As set forth in *In re Marzocchi et al.,* 169 USPQ 367 (CCPA 1971):

"[A] [s]pecification disclosure which contains teaching of manner and process of making and using the invention in terms corresponding to the scope to those used in describing and defining subject matter sought to be patented must be taken as in compliance with the enabling requirement of first paragraph of 35 U.S.C. 112 *unless there is reason to doubt the objective truth of statements contained therein which must be relied on for enabling support*; assuming that sufficient reasons for such doubt exists, a rejection for failure to teach how to make and/or use will be proper on that basis, such a rejection can be overcome by suitable proofs indicating that teaching contained in the specification is truly enabling." (emphasis added).

The term "prevent" in the present claims is considered to be comparable to the word "prophylaxis", and both circumscribe methods of absolute success. That is, in order to be enabled to practice the present invention, the skilled artisan would have to accept that by administering the presently claimed combination of active agents, the incidence of metabolic syndrome would be 0% and there would be a reasonable guarantee that metabolic syndrome would never develop. Such a situation is sufficiently unusual that data would need to be shown in order to establish that metabolic syndrome could be kept from ever occurring through the administration of the claimed active agent. Because absolute success is not reasonably possible with most diseases or disorders, especially a condition as complex and poorly understood as metabolic syndrome, the specification, which lacks an objective showing that such a disease could be prevented, is viewed as lacking an enabling disclosure of the same.

Here, the objective truth of the statement in claim 12, for example, that a condition such as metabolic syndrome may be prevented is doubted because the art expressly recognizes the complex nature and poor understanding of this syndrome and the predisposing factors that characterize this condition.

In this regard, Grundy ("Metabolic Complications of Obesity", Endocrine, 2000) is cited. Applicant's attention is drawn particularly to the abstract, which states, "The rising prevalence of obesity is accompanied by an increasing number of patients with the metabolic complications of obesity. The major complications come under the heading of the metabolic syndrome. This syndrome is characterized by plasma lipid disorders (atherogenic dyslipidemia), raised blood pressure, elevated plasma glucose, and a prothrombotic state. The clinical consequences of the metabolic syndrome are coronary heart disease and stroke, type 2 diabetes and its complications, fatty liver, cholesterol gallstones, and possible some forms of cancer. At the heart of the metabolic syndrome is insulin resistance...Obesity is the predominant factor leading to insulin resistance, although other factors play a role. The mechanistic link between insulin resistance and the metabolic syndrome is complex. The relationship is modulated by yet other factors, such as physical activity, body fat distribution, hormones, and a person's genetic polymorphic architecture. A better understanding of the molecular basis of this relationship is needed...In addition, understanding at the clinical level will lead to improved management of these complications."

Given that the art expressly acknowledges that the condition of metabolic syndrome and insulin resistance, the primary condition that characterizes metabolic syndrome and results in impaired glucose utilization, as being complex, the skilled artisan would have recognized that the state of the art with regard to metabolic syndrome is not well defined, and is, therefore, unpredictable, such that one of ordinary skill in the art would not accept on its face Applicant's statement that metabolic syndrome could be prevented because the pathophysiology of such a condition is not particularly well characterized. In light of such, the artisan would have required sufficient direction as to how the administration of the presently claimed combination of active agents could actually prevent the development of metabolic syndrome such that the artisan would have been imbued with at least a reasonable expectation of success. Such success would not have been reasonably expected give that absolute prevention is an outcome not reasonably expected by one of ordinary skill in the art and, to the artisan, the concept of a single agent, or even a combination of agents, that is effective in preventing the development of metabolic syndrome would have been unique and, thus, met with a great deal of skepticism.

Furthermore, given the breadth of conditions characterizing metabolic syndrome (i.e., plasma lipid disorders (atherogenic dyslipidemia), raised blood pressure, elevated plasma glucose, and a prothrombotic state), prevention or prophylaxis against metabolic syndrome would necessarily involve preventing each one or more of the conditions known to be associated with such a syndrome. Such a situation would require the skilled artisan to determine whether the active agents of the present claims are effective in preventing any one or more of these conditions and such a process would amount to undue experimentation, given the breadth of compounds claimed, the disparate nature of each of these conditions and the poor clinical understanding of metabolic syndrome in general.

Factor 4) Applicant has merely disclosed that the administration of the presently claimed active composition to a subject may prevent metabolic disorders of glucose utilization. Based on the discussion in Section 3 above, however, such disclosure clearly is not adequate direction or guidance as to how the proposed active composition of acetyl-L-carnitine and a mixture of polyphenols, including hydroxytyrosol, could be employed to accomplish the prevention of metabolic syndrome in a predictable manner.

Factor 5) The specification at paragraph [0015] merely discloses that use of the presently claimed active composition has activity in the prevention of disorders associated with tissue damage caused by free radicals due to environmental pollution; brain or myocardial lesions induced by free radicals following cerebral or myocardial ischemia and attendant reperfusion; diabetic or toxic neuropathies; or metabolic disorders of glucose utilization. Although Applicant discloses that prevention may be achieved, in the instant case, the specification does not provide guidance as to how one skilled in the art would accomplish the objective of preventing metabolic disorders of glucose utilization, of which metabolic syndrome is considered exemplary, or any one other of the above-mentioned conditions or how a patient could be kept from ever developing these disorders. Nor is there any guidance provided as to a specific protocol to be utilized in order to show the efficacy of the presently claimed active composition for the prevention of such a condition.

The Examiner acknowledges that the Office does not require the presence of working examples to be present in the disclosure of the invention (see MPEP §2164.02). However, in light of the state of the art, which recognizes the unpredictable nature of metabolic disorders of glucose utilization, of which metabolic syndrome is considered exemplary, there is no apparent data to support the contention that the use of the claim specified active composition could actually prevent such a metabolic condition by simply administering, by any method, an amount of the claimed active composition comprising acetyl-L-carnitine and a mixture of polyphenols, including hydroxytyrosol, since the present specification fails to enable one of ordinary skill in the art to practice the presently claimed invention insofar as it reads on the prevention of metabolic disorders of glucose utilization or any one or more of the other conditions encompassed by the present claims (i.e, tissue damage due to free radicals generated by environmental pollution; preventing brain or myocardial lesions induced by free radicals following cerebral or myocardial ischemia and attendant reperfusion; or diabetic or toxic neuropathies).

Factor 6) The burden of enabling the prevention of metabolic syndrome is much greater than that of enabling the treatment of the same condition. Since the present specification would not enable the skilled artisan to prevent metabolic syndrome, a clear burden of undue experimentation would be placed upon the skilled artisan in order to practice this aspect of the invention.

Factor 8) In view of the discussion of each of the preceding seven factors, the level of skill in this art is high and is at least that of a medical doctor with several years of experience in the art.

Summary

As the cited art and discussion of the above 8 factors establish, practicing the claimed method in the manner disclosed by Applicant would not imbue the skilled artisan with a reasonable expectation that prevention of metabolic disorders, of which metabolic syndrome is considered exemplary, or any one of the other conditions recited in present claim 12, could actually be achieved. In order to actually achieve prevention of such conditions, it is clear from the discussion above that the skilled artisan could not rely on Applicant's disclosure as required by 35 U.S.C. §112, first paragraph. Given that the art fails to recognize and Applicant has failed to demonstrate that metabolic syndrome or the other conditions recited in present claim 12 could actually be prevented, the skilled artisan would be faced with the impermissible burden of undue experimentation in order to practice this embodiment of the claimed invention. Accordingly, claims 12 and 14 are deemed properly rejected.

Claim Rejection - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 5 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 5 recites the limitation "The composition of claim 2 wherein the carnitine selected is the pharmacologically acceptable salt of L-carnitine or alkanoyl-L-carnitine selected from the group consisting of…" at lines 1-3 of the claim. There is insufficient antecedent basis for the limitation "or alkanoyl-L-carnitine…" in claim 5, since any reference to such a compound in the claim from which it depends (i.e., claim 2) is noticeably absent. It is unclear how Applicant intends claim 5 to limit the presently claimed subject matter. As a result, the claim fails to meet the tenor and express requirements of 35 U.S.C. 112, second paragraph, and is properly rejected for rendering the scope of the claim indefinite.

For the purposes of examination and the application of prior art, claim 5 will be interpreted to further limit the subject matter of claim 2 insofar as it reads upon pharmacologically acceptable salts of L-carnitine.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 6 and 8 are rejected under 35 U.S.C. 102(a) or 35 U.S.C. 102(e) as being anticipated by Crandall (U.S. Patent No. 6,333,057; December 2001) in light of Saija et al. ("In Vitro Evaluation of the Antioxidant Activity and Biomembrane Interaction of the Plant Phenols Oleuropein and Hydroxytyrosol", *International Journal of Pharmaceutics*, 1998), cited to show a fact.

In accordance with the MPEP at §2131.01, it is proper to rely upon a secondary reference for a rejection under 35 U.S.C. 102 to show that a characteristic not expressly disclosed by the reference is necessarily present.

Crandall teaches a composition for topical application to the scalp (considered to meet Applicant's limitation of "transdermally administrable form" as recited in present claim 8; col.4, lines 32-42) comprising acetyl carnitine or acetyl-L-carnitine hydrochloride (considered to meet Applicant's limitation of "acetyl-L-carnitine or a pharmacologically acceptable salt thereof" as recited in present claim 1; col.3, lines 37-40 and col.4, lines 49-52) and coenzyme Q (col.4, lines 49-52; see present claim 6) each in therapeutically effective amounts (considered to meet Applicant's limitation of an "effective weight ratio" as recited in present claim 1, since the fact that each compound is present in an effective amount necessarily means that a comparison of the amounts would result in an effective "ratio" of said amounts; col.4, lines 63-67) in combination with olive oil (col.4, lines 49-60; see present claim 1) as a delivery vehicle and/or penetrating agent, and further comprising antioxidants (col.6, lines 38-40; see present claim 6), vitamin E (considered to meet Applicant's limitation of a "vitamin" as recited in present claim 6; col.6, lines 21-24) or a preservative, such as potassium sorbate (considered to meet Applicant's limitation of a "mineral substance" as recited in present claim 6; col.6, lines 20-21).

Saija et al. is relied upon to show that olive oil is known to contain the phenol compounds oleuropein and hydroxytyrosol. Thus, such compounds are necessarily present in the composition disclosed by Crandall because the very presence of olive oil would necessarily mean that the phenolic compounds oleuropein and hydroxytyrosol contained within such an oil were also present. Furthermore, the fact that both oleuropein and hydroxytyrosol are both necessarily present in the composition supports the fact that Applicant's limitation that a "mixture of polyphenols containing hydroxytyrosol" is met by the teachings of Crandall.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

I Claims 1-6 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Crandall (U.S. Patent No. 6,333,057; December 2001) in light of Saija et al. ("In Vitro Evaluation of the Antioxidant Activity and Biomembrane Interaction of the Plant Phenols Oleuropein and Hydroxytyrosol", *International Journal of Pharmaceutics*, 1998), cited to show a fact, and further in view of Cavazza (WO 00/11968; 2000) and Shug (U.S. Patent No. 5,240,961; 1993).

Crandall teaches a composition for topical application to the scalp (considered to meet Applicant's limitation of "transdermally administrable form" as recited in present claim 8; col.4; lines 32-42) comprising acetyl carnitine or acetyl-L-carnitine hydrochloride (considered to meet Applicant's limitation of "acetyl-L-carnitine or a pharmacologically acceptable salt thereof" as recited in present claim 1; col.3, lines 37-40 and col.4, lines 49-52) and coenzyme Q (col.4, lines 49-52; see present claim 6) each in therapeutically effective amounts (considered to meet Applicant's limitation of an "effective weight ratio" as recited in present claim 1, since the fact that each compound is present in an effective amount necessarily means that a comparison of the amounts would result in an effective "ratio" of said amounts; col.4, lines 63-67) in combination with olive oil (col.4, lines 49-60; see present claim 1) as a delivery vehicle and/or penetrating agent, and further comprising antioxidants (col.6, lines 38-40; see present claim 6), vitamin E (considered to meet Applicant's limitation of a "vitamin" as recited in present claim 6; col.6, lines 21-24) or a preservative, such as potassium sorbate (considered to meet Applicant's limitation of a "mineral substance" as recited in present claim 6; col.6, lines 20-21).

Saija et al. is relied upon to show that hydroxytyrosol and oleuropein are necessarily present in olive oil and, thus, meet Applicant's limitation of a "mixture of polyphenols containing hydroxytyrosol" as taught by Crandall.

The differences between the Crandall reference and the presently claimed subject matter lie in that the reference fails to teach:

(i) the use of acetyl-L-carnitine (see present claim 1) or an additional carnitine component, including L-carnitine, propionyl-L-carnitine, valeryl-L-carnitine, isovaleryl-L-carnitine (see present claim 2) or pharmacologically acceptable salts thereof; or

(ii) the particular weight ratio of components as recited in present claim 3.

However, the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains because:

(i) Although Crandall teaches acetyl carnitine in general or acetyl-L-carnitine hydrochloride, but is silent as to the particular use of the free base acetyl-L-carnitine or the additional use of L-carnitine, propionyl-L-carnitine, valeryl-L-carnitine, isovaleryl-L-carnitine, the use of such carnitine compounds would have been a matter well within the purview of the skilled artisan. Crandall teaches that the acetyl carnitine compounds disclosed by the reference must be capable of improving fatty acid metabolism by stimulation of cardiolipin, which affects the activity of the inner mitochondrial membrane, affecting its permeability and function for proton transport (see Crandall, col.3, lines 48-51).

In this regard, Cavazza (WO 00/11968; 2000) is cited. Cavazza teaches that carnitines, such as those specifically disclosed in the reference (i.e., acetyl-L-carnitine, L-carnitine or the alkanoyl-L-carnitine compounds, such as propionyl-L-carnitine, valeryl-L-carnitine, isovaleryl-L-carnitine, and pharmacologically acceptable salts thereof; see page 19, last paragraph-page 20, paragraph 1) produce energy via intra-mitochondrial beta-oxidation of fatty acids (page 2, paragraph 1) and that administration of the compound acetyl-L-carnitine was known in the art to reactivate mitochondrial activity, including the fatty acid beta-oxidation processes, by restoring normal cardiolipin concentrations in the mitochondria (see Cavazza, page 2, paragraph 6).

In light of such a teaching, it would have been obvious to the skilled artisan to employ acetyl-L-carnitine itself in the composition disclosed by Crandall because such a compound was known to have the same functional properties as those attributed to the specific acetyl carnitine compounds disclosed by Crandall. Such a person would have been motivated to use acetyl-L-carnitine or its pharmacologically acceptable salts because such a compound would have been reasonably expected to be function in the same or substantially similar manner to those carnitine compounds expressly taught by the reference, and, thus, use of such would not result in any loss of antioxidant function or efficacy of the composition.

Similarly, the additional use of a carnitine compound, such as L-carnitine, propionyl-L-carnitine, valeryl-L-carnitine or isovaleryl-L-carnitine or their pharmacologically acceptable salts, would also have been well within the purview of the skilled artisan because it was known in the art that exogenous administration of carnitine compounds was capable of restoring normal cellular function, such as energy production by mitochondrial beta-oxidation of fatty acids and branched-chain amino acids (see Cavazza, page 1, paragraph 4 and page 2, paragraph 1). Thus, it would have been obvious to the skilled artisan that concomitant administration of another carnitine component in addition to the acetyl-L-carnitine would have potentiated the normalizing effect on mitochondrial beta-oxidation of fatty acids and, thus, would have reduced the overall presence of oxidants (page 2, paragraph 5).

(ii) The determination of the optimum weight ratios of the presently claimed active agent(s) would have been a matter well within the purview of one of ordinary skill in the art. Such a determination would have been made in accordance with a variety of factors, such as the age, weight, sex, diet and medical condition of the patient, severity of the disease, the route of administration, pharmacological considerations, such as the activity, efficacy, pharmacokinetics and toxicology profiles of the particular compound employed, whether a drug delivery system is utilized and whether the compound is administered as part of a drug combination. Thus, the weight ratios that would have actually been employed would have varied widely and, in the absence of evidence to the contrary, the currently claimed specific weight ratios are not seen to be inconsistent with those that would have been determined by the skilled artisan.

Applicant's attention is drawn to MPEP at §2144.05, which states, "The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages...Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." Although the present claims are drawn to weight ratios and not percentages, such a motivation is nonetheless relevant.

II Claims 1-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cavazza (U.S. Patent No. 6,365,622; 2002) or Cavazza (WO 00/11968; 2000), in view of Saija et al. ("In Vitro Evaluation of the Antioxidant Activity and Biomembrane Interaction of the Plant Phenols Oleuropein and Hydroxytyrosol", *International Journal of Pharmaceutics*, 1998).

The rejection is set forth below as it applies to Cavazza (U.S. Patent No. 6,365,622; 2002). However, the rejection is entirely applicable to Cavazza (WO 00/11968; 2000), but for the differences the citation of page and line numbers. It is further noted that Cavazza (WO 00/11968; 2000) is considered to be the equivalent of Cavazza (U.S. Patent No. 6,365,622; 2002), since the WO document is the publication of the PCT application from which the '622 is derived.

Cavazza teaches a composition formulated for oral administration as a dietary supplement (claim 7 at col.12, lines 15-16; see present claims 7-8) in solid, semi-solid or liquid form (claim 9 at col.12, lines 20-21; see present claim 9) or in the form of tablets, lozenges, pills, capsules, granulates, syrups, injection or drops (claims 10-11 at col.12, lines 22-26; see present claims 10-11), parenteral, rectal or transdermal administration (claim 8 at col.12, lines 17-19; see present claim 8) comprising acetyl-L-carnitine or a pharmacologically acceptable salt thereof (claim 1 at col.11, lines 48-51; see present claims 1 and 4), optionally in combination with at least one other (considered to meet Applicant's limitation of "mixtures thereof" as recited in present claim 2) carnitine compound selected from L-carnitine or an alkanoyl-L-carnitine, such as propionyl-L-carnitine, valeryl-L-carnitine, isovaleryl-L-carnitine or pharmacologically acceptable salts thereof (claim 2 at col.11, lines 52-56; see present claims 2 and 5) and further comprising alpha-lipoic acid (claim 1 at col.11, lines 48-51), wherein the weight ratio of acetyl-L-carnitine to alpha-lipoic acid is 100:1 to 1:10 (claim 3 at col.11, lines 57-58; see present claims 3 and 15) and the composition may further comprise vitamins, coenzymes, mineral substances or antioxidants (claim 6 at col.12, lines 12-14; see present claim 6). Cavazza teaches the pharmacologically acceptable salts of the carnitine component may be any one of chloride, bromide, iodide, aspartate, acid aspartate, citrate, acid citrate, tartrate, phosphate, acid phosphate, fumarate, acid fumarate, glycerophosphate, glucose phosphate, lactate, maleate, acid maleate, orotate, oxalate, sulphate, acid sulphate, trichloroacetate, trifluoroacetate or methanesulphate (claims 4-5 at col.11, line 59-col.12, line 2; see present claims 4-5), and that the disclosed composition may be administered for the treatment of diseases brought about by the presence of free radicals due to environmental pollution; brain or myocardial damages induced by free radicals following cereal or myocardial ischemia and attendant reperfusion; toxic or diabetic neuropathies, metabolic disorders of glucose utilization or atherosclerotic lesions and tissue proliferative processes (claims 13-15 at col.12, lines 43-62; see present claim 13).

The differences between the Cavazza reference and the presently claimed subject matter lie in that the reference fails to teach the use of a mixture of polyphenols containing hydroxytyrosol.

However, the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains because hydroxytyrosol and oleuropein, both components of olive oil, were known in the art to have powerful antioxidant activity and, thus, would have been useful for the same therapeutic objectives of treating diseases associated with the presence of free radicals as disclosed by Cavazza.

In this regard, Saija et al. ("In Vitro Evaluation of the Antioxidant Activity and Biomembrane Interaction of the Plant Phenols Oleuropein and Hydroxytyrosol", *International Journal of Pharmaceutics*, 1998) is cited. Saija et al. teaches hydroxytyrosol and oleuropein, both compounds derived from olives or olive oil, as having good free radical scavenger ability and antioxidative effects (see abstract, for example). Saija et al. further teaches that hydroxytyrosol scavenges aqueous peroxyl radicals near the membrane surface and oleuropein scavenges chain-propagating lipid peroxyl radicals within the cell membranes (page 131, column 2, second paragraph). Saija et al. additional discloses that the olive phenols oleuropein and hydroxytyrosol act as powerful antioxidants against lipid peroxidation in phospholipid bilayers induced by aqueous oxygen radicals. In view of this activity, Saija et al. concludes that such compounds may be important in the treatment of human diseases accompanied by free radical injury (page 132, column 1, second paragraph).

Thus, in light of such a teaching, the use of the phenolic olive compounds hydroxytyrosol and oleuropein in the composition disclosed by Cavazza would have been *prima facie* obvious to one of ordinary skill in the art because it was well known in the art that such compounds shared the same common antioxidative function and, thus, would have been reasonably expected to exert the same or substantially similar free radical scavenging properties, as supported by the teachings of Saija et al., as the acetyl-L-carnitine and/or lipoic acid components of the composition disclosed by Cavazza. Motivation to administer hydroxytyrosol and oleuropein flows logically from the efficacy demonstrated in the prior art as potent antioxidative compounds. The skilled artisan would have reasonably concluded that the antioxidative effect exhibited by hydroxytyrosol and oleuropein would have shared similar efficacy in treating the disorders and conditions associated with free radicals as taught by Cavazza since each of these compounds was known in the art to be highly effective in scavenging cellular free radicals (see Saija et al., especially page 132, column 1, paragraph 2) and, thus, would have achieved, at minimum, additive, if not synergistic, effects when combined. It is further noted that in the absence of evidence to the contrary, it is generally _prima facie_ obvious to use in combination two or more agents that have previously been used separately for the same purpose. See *In re Kerkhoven*, 205 USPQ 1069 (CCPA).

Double Patenting

Obviousness-Type Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-11 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the composition claims of U.S. Patent Application Nos. 10/190,043 and 10/165,411 and are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the composition claims of U.S. Patent Nos. 6,197,308; 6,416,808; 6,165,475; and 6,936,287. This rejection is directed solely to the claims of the above-cited patent applications that define compositions, i.e., the same statutory category of invention.

Due to the number of applicable different patents and patent applications, a detailed analysis of why the presently claimed subject matter would have been an obvious variation over each one of the applicable claims in the various patent applications is not presented, but the rejection set forth below is representative of and applicable to all of the above-cited patent applications, but for the differences in claim numbering.

Claims 1-11 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claims 28-30 of U.S. Patent Application No. 10/190,043, in view of Cavazza (U.S. Patent No. 6,365,622; 2002).

For the following reasons, the presently claimed subject matter would have been obvious not only over such claims, but over each of the applicable claims of the remaining U.S. Patent

Applications cited above.

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claims because the examined claims is either anticipated by, or would have been obvious over, the reference claims.

Although the conflicting claims are not identical, the claims of the instant patent application and those of the copending patent application are not considered patentably distinct from each other because the copending claims render the present claims obvious.

The copending claims clearly provide for an oral composition comprising a mixture of olive polyphenols that contains hydroxytyrosol. While the copending claims are silent as to the use of acetyl-L-carnitine or another carnitine compound, the combination of the hydroxytyrosol/oleuropein components with acetyl-L-carnitine or salts thereof or any one of L-carnitine, propionyl-L-carnitine, valeryl-L-carnitine or isovaleryl-L-carnitine or salts thereof would have been *prima facie* obvious to the skilled artisan in light of the fact that acetyl-L-carnitine was known to maintain mitochondrial activity, which protects against an increase in circulating oxidants from reduced mitochondrial activity (see Cavazza, col.1, lines 30-35; col.1, lines 56-67) and, thus, exerts the same "antioxidant" effect as that of hydroxytyrosol and oleuropein of the copending claims.

Similarly, the additional use of a carnitine compound, such as L-carnitine, propionyl-L-carnitine, valeryl-L-carnitine or isovaleryl-L-carnitine or their pharmacologically acceptable salts, would also have been well within the purview of the skilled artisan because it was known in the art that exogenous administration of carnitine compounds was capable of restoring normal cellular function, such as producing energy by mitochondrial beta-oxidation of fatty acids and branched-chain amino acids (see Cavazza, col.1, lines 30-35 and col.1, line 59-col.2, line 12). Thus, it would have been obvious to the skilled artisan that concomitant administration of another carnitine component in addition to the acetyl-L-carnitine would have potentiated the normalizing effect on mitochondrial beta-oxidation of fatty acids and, thus, would have reduced the overall presence of oxidants (col.1, line 30-col.2, line 12).

Motivation to administer the carnitine compounds of the present claims flows logically from the efficacy demonstrated in the prior art as potent antioxidative compounds. The skilled artisan would have reasonably concluded that the antioxidative effect exhibited by such carnitine compounds would have achieved, at minimum, additive, if not synergistic, effects when combined with the hydroxytyrosol/oleuropein compounds of the copending claims. It is further noted that in the absence of evidence to the contrary, it is generally *prima facie* obvious to use in combination two or more agents that have previously been used separately for the same purpose. See *In re Kerkhoven*, 205 USPQ 1069 (CCPA).

Furthermore, the determination of the optimum weight ratios, formulations, and route of administration would have each been matters well within the purview of the skilled artisan. Such a determination would have been made in accordance with a variety of factors, including, but not limited to, the amount to be administered, patient compliance with the regimen, toxicological considerations, such as adverse effects and tolerance to the regimen, pharmacological considerations, and the age, weight, sex, diet and medical condition of the patient.

Accordingly, rejection of claims 1-11 of the present application is deemed proper over claims 28-30 of U.S. Patent Application No. 10/190,043, and also over the applicable claims of each one of the above-indicated patent applications, as claiming obvious and unpatentable variants thereof.

Conclusion

Rejection of claims 1-15 is deemed proper.

No claims of the present application are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leslie A. Royds whose telephone number is (571)-272-6096. The examiner can normally be reached on Monday-Friday (8:30 AM-6:00 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (571)-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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